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Synthesis and Resolution of Substituted [5]Carbohelicenes

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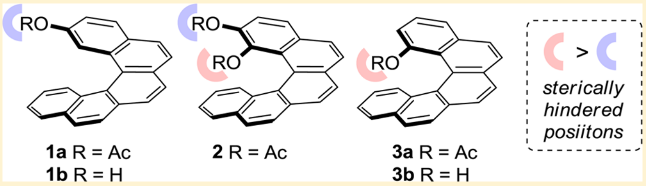
S Supporting Information

ABSTRACT: Three types of racemic [5]helicenyl acetates (**1a**, **2**, and **3a**) were synthesized. The synthesis of **2** was achieved by regioselective oxidation using *o*-iodoxybenzoic acid. The enzymatic kinetic resolution of **1a**−**3a** was studied. The conversion with the highest rate and *ee* was obtained using **1a** as the substrate and lipase Amano PS-IM as the enzyme. The two enantiomers of 1-[5]helicenol **3b** were separated using (1*S*)-10-camphorsulfonyl chloride as the chiral resolving agent.



[*n*]Helicene derivatives are *ortho*-annulated aromatic rings showing helical chirality. Enantiopure [*n*]helicenes with $n \geq 6$ and [4]- and [5]-helicenes with a substituent on the interior side of the helical aromatic framework can be isolated at room temperature because of their high configurational stability.[1] Therefore, chiral-functionalized helicenes have received considerable attention for applications in chiral materials, asymmetric catalysis, and chiral recognition of biomolecules.[2] For these purposes, the preparation of enantiomerically pure helicenes is required.

The enzymatic transformation of organic substrates is well-known as a method for the preparation of optically active compounds. Enzymes efficiently catalyze a broad range of chemical reactions under mild and environmentally friendly conditions, often with very high enantioselectivity. Although several studies have investigated the lipase-catalyzed acylation of thiaheterohelicenes with primary alcohols,[3] lipase-catalyzed direct deacylation of phenolic acetates has been reported only when [5]helicene-like 4-acetate is used as a substrate.[4] In this context, we recently reported the synthesis of 1-functionalized [5]helicenes and the separation of the enantiomers using chiral HPLC.

In this work, we focused on the synthesis of [5]helicenes with functional groups on the sterically hindered 1- and/or 2-position of the helix and the development of protocols for their optical resolution. Herein, we report a concise synthesis of [5]helicenyl acetates (*rac*-**1a**−**3a**), their lipase-catalyzed kinetic resolution, and the optical resolution of (±)-1-[5]helicenol (**3b**) using a resolving agent. Furthermore, to gain a deeper insight into the reactivity of lipase, we conducted computational modeling studies using [5]helicenes.

Initially, (±)-2-[5]helicenyl acetate (*rac*-**1a**) was synthesized via the route shown in Scheme 1. Synthesis of alkyne **8**, a precursor of *rac*-**1a**, proceeded via the Vilsmeier−Haack reaction of 7-methoxy-1-tetralone **4** to afford *β*-chloroacrolein **5** in 91% yield.[5] Suzuki-Miyaura cross-coupling of **5** with 1-naphthylboronic acid afforded coupling product **6** in quantitative yield. The subsequent oxidative aromatization of **6** with dichlorodicyanobenzoquinone (DDQ) gave compound **7** in quantitative yield. Finally, the Ohira-Bestmann modification of the Seyferth-Gilbert method afforded **8** in 93% yield. Cycloisomerization of **8** with 5 mol % $PtCl_2$ at 85 °C in toluene resulted in the formation of (±)-2-methoxy[5]helicene (*rac*-**1c**) as the sole product. Its bromide, *rac*-**1d**, was characterized by X-ray crystallography to confirm its structure (Figure 1). *Rac*-**1c** was then readily converted by demethylation using BBr_3 to (±)-2-[5]helicenol (*rac*-**1b**) in quantitative yield. This procedure may be employed to afford *rac*-**1b** in 63% overall yield from **4**.

For the synthesis of (±)-1,2-[5]helicenyl diacetate (*rac*-**2**), *rac*-**1b** was treated with *o*-iodoxybenzoic acid (IBX) in DMF to afford the desired [5]helicene *o*-quinone (*rac*-**9**),[6] which was converted to *rac*-**2** in 68% yield by a sequence of reduction and acetylation reactions (Scheme 2). The structure of *rac*-**9** was confirmed by COSY, HMBC, and NOESY spectra. A computational DFT study was performed for the regioselective IBX oxidation of *rac*-**1b** (Figure 2). Based on previous studies,[7] *rac*-**1b** reacts with IBX to produce aryloxy-λ^5-iodane intermediates **IM1*a*/1b**, which transfer oxygen to the *ortho*-site via a sigmatropic-like [2,3]-rearrangement. During this process, the iodine(V) atom is reduced to the λ^3-iodanyl species **IM2*a*/2b**, forming *o*-quinone. Thus, the regioselectivity in this reaction could be determined by the transition state of the [2,3]-rearrangement process. Indeed, the DFT results show that the [2,3]-rearrangement step from **IM1*a*/1b** would give **IM2*a*/2b** via **TS1*a*/1b**, involving energy barriers of 2.4 and 4.0 kcal mol^{-1}, respectively. Thus, the difference in the computed free energy barriers (1.6 kcal mol^{-1}) for the internal positions of the oxidation processes is in good agreement with the experimental result.[8]

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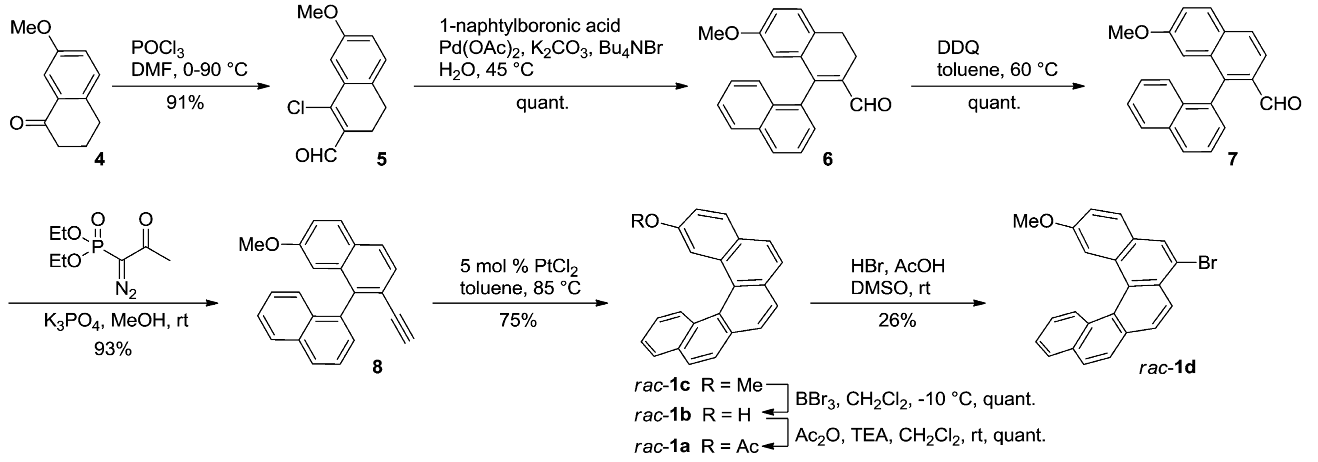
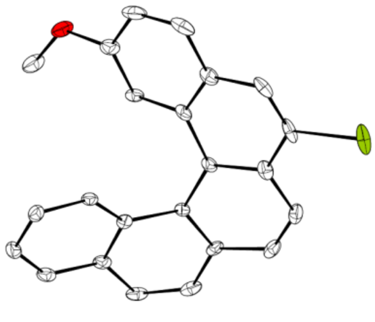
Scheme 1. Synthesis of 2-[5]Helicenyl Acetate 1a

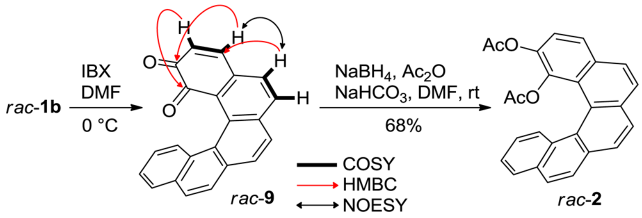




1d

Figure 1. ORTEP drawing of **1d** with 50% ellipsoid probability.

Scheme 2. Synthesis of 1,2-[5]Helicenyl Diacetate 2



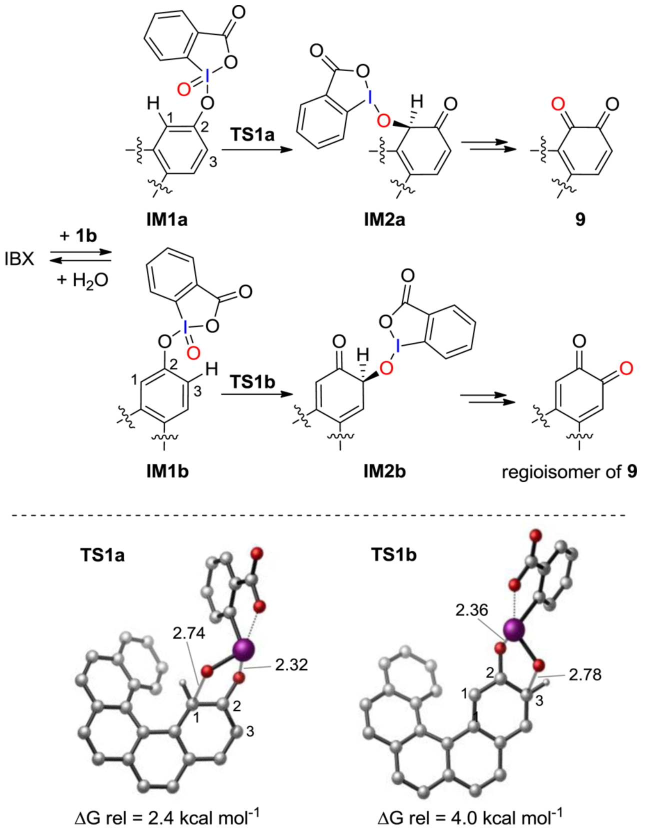


Figure 2. Computational investigation of the [2,3]rearrangement pathway. The relative free energies (kcal mol^{-1}, at 298 K) for the stationary points were calculated using B3LYP with the 6-31G* basis set for O, C, and H, and LANL2DZ for iodine. Most of the hydrogen atoms have been omitted for clarity. IM = intermediate, TS = transition state.

(±)-1-[5]Helicenyl acetate (*rac*-**3a**) was synthesized by our previous procedure (see the Supporting Information).[1a]

Next, we examined the hydrolysis of *rac*-**1a**−**3a** using several different enzymes in *tert*-butylmethyl ether (MTBE) containing water. The enzymatic hydrolysis of *rac*-**1a** was performed using lipases at 30 °C, and the reaction course was monitored by chiral HPLC (Daicel, Chiral IA column). The results of the kinetic resolutions are summarized in Table 1.

Hydrolysis of *rac*-**1a** in the presence of Amano PS proceeded to give (+)-(*P*)-**1b** with 38% *ee* in 59% yield, and (−)-(*M*)-**1a** of 35% *ee* was recovered in 41% yield (entry 1).[9] Furthermore, Amano PS IM (where IM indicates that the lipase is immobilized on diatomaceous earth) showed higher reactivity than Amano PS. Other lipases such as Amano M, F-Ap15, CAL, Amano AK, and Amano AYS showed low reactivity and/or low enantioselectivity when *rac*-**1a** was used as a substrate (entries 3−7). Although *rac*-**1a** showed good conversion yield at 30 °C with Amano PS IM, its enantioselectivity was low (entry 2), probably because of the racemization of the product under the reaction conditions employed. In fact, the Gibbs's free energy barriers for racemization ($\Delta G^{\ddagger}$) were found to be 23.0 kcal mol^{-1} ($k = 5.2 \times 10^{-3}$ min^{-1}, $t_{1/2}$ = 133 min at 303 K) and 23.2 kcal mol^{-1} ($k = 3.5 \times 10^{-3}$ min^{-1}, $t_{1/2}$ = 198 min at 303 K) for **1a** and **1b**, respectively.[10] In order to avoid racemization, we changed the amount of lipase used and the reaction temperature. As a result, racemization was suppressed, and **1a** and **1b** were obtained with good enantioselectivity (entries 8−10). The hydrolysis of the configurationally stable diacetate *rac*-**2** gave inseparable mixtures (Figure S2), and these compounds

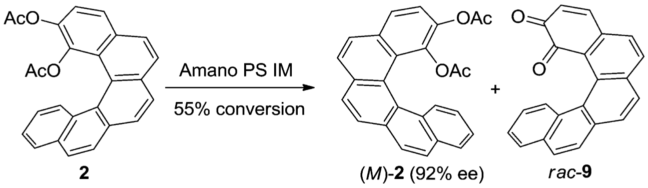
Table 1. Optical Resolution of 1a by Lipase Catalysts[a,b]

entry	enzyme[c]	time (h)	*ee* (%) (*P*)-**1b**[d]	*ee* (%) (*M*)-**1a**[d]	*c* (%)
1	Amano PS	24	38	35	59
2	Amano PS IM	4	35	45	59
3	Amano M	18	23	18	56
4	F-Ap 15	48	4	2	51
5	CAL	72	—	—	—
6	Amano AK	72	—	—	—
7	Amano AYS	72	—	—	—
8[e]	Amano PS IM	0.2	76	29	27
9[e]	Amano PS IM	0.5	67	67	51
10[e]	Amano PS IM	1	52	92	65

[a] General conditions: 1 mmol (5 mg) of substrate, 5 mg of lipase in 1 mL of MTBE (0.25% H_2O), 30 °C. [b] The conversion values and enantiomeric excesses were determined by HPLC using a Chiralcel IA column. [c] Amano PS: *Burkholderia cepacia* lipase; Amano M: *Mucor javanicus* lipase; F-Ap 15; *Rhizopus oryzae* lipase; CAL: *Candida antarctica* lipase; Amano AK: *Pseudomonas fluorescens* lipase; Amano AYS; *Candida rugosa* lipase. [d] Absolute configurations were determined using their circular dichroism spectra. [e] 50 mg of lipase was used at 20 °C.

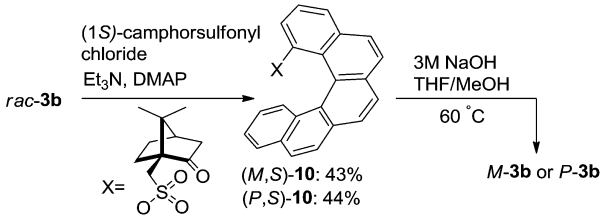
were converted readily into **9** by treatment with 1 M NaOH (Figure S3 and Scheme 3). Helicene catechol would be air-sensitive and undergo oxidation to give corresponding **9**.[6] Helicene **3a** is recovered with 92% *ee* at 55% conversion, while a solution of isolated **9** exhibited no optical activity due to the low racemization barrier (ΔG = 19.4 kcal mol^{-1} by DFT).[11]

Scheme 3. Optical Resolution of 2 by Amano PS IM



The configurationally stable acetate *rac*-**3a** was not hydrolyzed at all by lipases. This may be due to the steric hindrance caused by the bulky helicene scaffold. Next, *rac*-**3a** was resolved to each enantiomer by using (1*S*)-10-camphorsulfonyl chloride as a resolving agent.[12] Treatment of *rac*-**3a** with (1*S*)-10-camphorsulfonyl chloride and Et_3N in CH_2Cl_2 at room temperature led to a mixture of two diastereomeric helicene camphorsulfonates, (*M*,*S*)-**10** and (*P*,*S*)-**10**, in 87% combined yield (Scheme 4). The diastereomers were separated on a silica gel column to give (*M*,*S*)-**10** (43%) and (*P*,*S*)-**10** (44%). The subsequent desulfonylation generated enantiomerically pure (*M*)-**3b** and (*P*)-**3b**. The relative configurations of diastereomers (*M*,*S*)-**10** and (*P*,*S*)-**10** were confirmed by X-ray crystallography (Figure 3).

Scheme 4. Enantiomeric Resolution of 3b with (1*S*)-10-Camphorsulfonyl Chloride



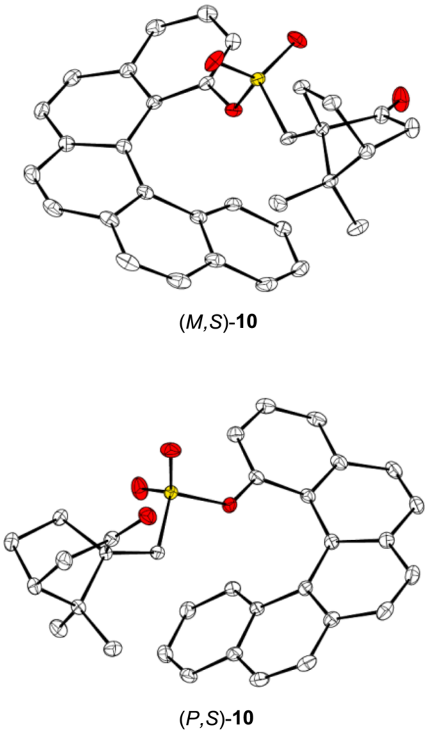


Figure 3. ORTEP drawing of (***M*,*S***)-10 and (***P*,*S***)-10 with 50% ellipsoid probability.

Next, we performed Amano PS lipase (PDB code 1YS1) docking studies in silico using transition state analogues ((*P*)-**1**′ and (*P*)-**2**′) to understand the interactions between these molecules and lipase (Figure 4). The docking calculations were performed using *MacroModel*, and it was predicted that the phosphine oxide[13] (*P*)-intermediate forms hydrogen bonds with three amino acid residues, His286, Gln88, and Leu17, which stabilize the tetrahedral intermediate. It is noteworthy that in both intermediates the significant intramolecular H-bond interactions of the lipase are not interrupted.

In summary, after developing the synthesis of racemic [5]helicenyl acetates (**1a**−**3a**), we demonstrated their lipase-catalyzed kinetic resolution. The reactivity of [5]helicene toward enzymatic hydrolysis was found to be highly dependent on the position of the acetate group, as the enzymatic hydrolysis of substrate **3a** did not occur. We expect that this optical resolution protocol will prove to be useful in the synthesis of chiral [5]helicene compounds.

■ EXPERIMENTAL SECTION

General Information. All reagents and solvents were purchased from commercial sources and were used as received unless otherwise noted. Reagent grade solvents (CH_2Cl_2, toluene, DMSO, DMF) were distilled prior to use. Reactions were monitored by TLC (silica gel 60 F_{254}, 0.25 mm) analysis. Flash column chromatography was performed on flash silica gel 60N (spherical neutral, particle size 40−50 μm). HPLC analyses were conducted with a UV detector and a chiral column: Daicel Chiralpak IA (4.6 mm × 250 mm). ^1H and ^{13}C NMR were recorded in $CDCl_3$ as solvent at ambient temperature on a 400 or 500 MHz NMR spectrometer (100

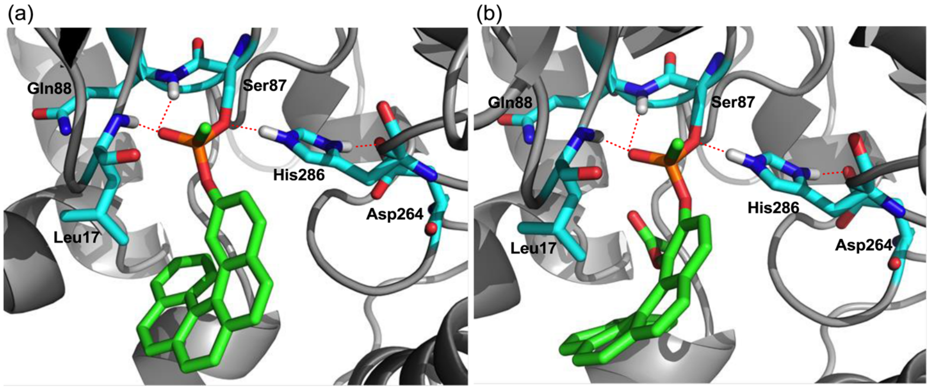


Figure 4. Modeled complexes of Amano PS with transition state analogue ((*P*)-**1′** (a) and (*P*)-**2′** (b)) showing the front view of the active site.

or 125 MHz for ^{13}C NMR). Chemical shifts were reported in parts per million (ppm) relative to internal tetramethylsilane (δ 0.00 ppm) or CDCl$_3$ (δ 7.26 ppm) for ^{1}H NMR and CDCl$_3$ (δ 77.0 ppm) for ^{13}C NMR. Coupling constants were reported as *J* values in Hertz (Hz). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), dd (double of doublet), ddd (doublet of doublet of doublets), br (broad), and m (multiplet). Infrared spectra of neat samples were recorded in ATR (attenuated total reflectance) mode using an FT-IR instrument. HRMS were recorded on a ESI-TOF spectrometer. Optical rotations were measured with a polarimeter using a 0.5 dm cell. CD measurements were performed on a spectropolarimeter with an optical path length of 1.0 mm.

Dibenzo[*c*,*g*]phenanthren-9-yl acetate (1a). To a stirred solution of **1b** (0.20 g, 0.68 mmol) in CH$_2$Cl$_2$ (20 mL) at 0 °C under an argon atmosphere were added triethylamine (0.47 mL, 3.34 mmol) and acetic anhydride (0.13 mL, 1.36 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 2 h. The reaction was quenched with water at 0 °C. The aqueous layer was extracted with CH$_2$Cl$_2$. The organic layers were combined, washed with water and brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with hexane-EtOAc (9:1) to afford **1a** (0.23 mg, quant.) as a pale yellow solid. (*P*)-(+)-**1a** $[\alpha]_D^{20}$ = +1860 (*c* 8.2 × 10^{-3}, CHCl$_3$), (*M*)-(−)-**1a** $[\alpha]_D^{20}$ = −1860 (*c* 8.2 × 10^{-3}, CHCl$_3$); mp =166−167 °C; IR (neat, cm^{-1}) 1758, 1368, 1206, 1170, 1033, 915, 848, 763, 747, 672, 663; UV−vis (CHCl$_3$): λ_{max} (log ε) = 332 (4.16), 305 (4.43), 269 (4.51), 240 (4.44) nm; ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.55 (d, *J* = 8.5 Hz, 1H), 8.19 (d, *J* = 1.0 Hz, 1H), 7.95−7.83 (m, 8H), 7.51 (ddd, *J* = 8.0, 6.9, 1.1 Hz 1H), 7.32 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.25 (dd, *J* = 8.7, 2.3 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 169.7, 147.5, 132.7, 132.6, 132.3, 131.6, 130.7, 130.3, 129.2, 128.9, 127.8, 127.7, 127.6, 127.2, 127.1, 127.0, 126.7, 126.4, 126.3, 124.9, 121.2, 120.7, 21.1; HRMS (ESI, Pos) *m*/*z*: [M + Na]$^+$ calcd for C$_{24}$H$_{16}$O$_2$Na 359.1043, found 359.1075.

Dibenzo[*c*,*g*]phenanthren-9-ol (1b). To a solution of **1c** (0.97 g, 3.15 mmol) in CH$_2$Cl$_2$ (31 mL) at −10 °C under an argon atmosphere was added dropwise a 1.0 M solution of BBr$_3$ in CH$_2$Cl$_2$ (6.3 mL, 6.30 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 3 h. The reaction was quenched with water at 0 °C. The aqueous layer was extracted and with CH$_2$Cl$_2$. The organic layers were combined, washed with water and brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with hexane−EtOAc (8:1) to afford **1b** (0.92 g, quant.) as a pale yellow solid. (*P*)-(+)-**1b** $[\alpha]_D^{20}$ = +2642 (*c* 2.1 × 10^{-2}, CHCl$_3$), (*M*)-(−)-**1b** $[\alpha]_D^{20}$ = −2811 (*c* 2.0 × 10^{-2}, CHCl$_3$); mp =188−191 °C; IR (neat, cm^{-1}) 3500, 2969, 1438, 1056, 1033, 1011, 873, 841, 829, 764, 714, 697; UV−vis (CHCl$_3$): λ_{max} (log ε) = 337 (4.21), 305 (4.36), 271 (4.45), 241 (4.50) nm; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.55 (d, *J* = 8.6 Hz,1H), 7.96−7.85 (m, 8H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.13 (dd, *J* = 8.8, 2.5 Hz, 1H), 4.93 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_{3,}$): δ 152.6, 132.8, 132.7, 132.1, 132.1, 130.3, 129.7, 129.3, 127.6, 127.3, 127.3, 127.1, 126.5, 126.1, 125.9, 124.2, 124.1, 112.5; HRMS (ESI, Pos) *m*/*z*: [M + Na]$^+$ calcd for C$_{22}$H$_{14}$NaO 317.0937, found 317.0944.

9-Methoxydibenzo[*c*,*g*]phenanthrene (1c). A solution of **8** (3.45 g, 11.18 mmol) and PtCl$_2$ (0.15 g, 5 mol %) in toluene (56 mL) was stirred at 85 °C for 8 h under an argon atmosphere. After cooling to room temperature, the solvent was evaporated and the residue was purified by flash column chromatography on silica gel eluting with hexane−EtOAc (95:5) to afford **1c** (2.58 g, 75%) as a pale yellow solid. (*P*)-(+)-**1c** $[\alpha]_D^{20}$ = +2463 (*c* 4.5 × 10^{-2}, CHCl$_3$), (*M*)-(−)-**1c** $[\alpha]_D^{20}$ = −2258 (*c* 1.6 × 10^{-3}, CHCl$_3$); mp =144−145 °C; IR (neat, cm^{-1}) 2966, 1231, 1054, 1033, 1011, 873, 842, 747; UV−vis (CHCl$_3$): λ_{max} (log ε) = 401 (2.81), 381 (3.63), 304 (4.41), 270 (4.48), 242 (4.53) nm; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.46 (d, *J* = 8.6 Hz,1H), 7.97−7.84 (m, 8H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.51 (t, *J* = 7.1 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.17 (dd, *J* = 8.8, 2.6 Hz, 1H), 3.49 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 156.5, 132.7, 132.6, 132.1, 131.9, 130.2, 129.7, 129.3, 127.9, 127.6, 127.4, 127.2, 127.1, 127.0, 126.4, 126.2, 126.1, 124.1, 124.0, 118.0, 109.2, 54.8; HRMS (ESI, Pos) *m*/*z*: [M + Na]$^+$ calcd for C$_{23}$H$_{16}$NaO 331.1093, found 331.1093.

2-Bromo-12-methoxydibenzo[*c*,*g*]phenanthrene (1d). Compound **1d** was prepared according to Majetich's procedure.[14] To a solution of **1c** (30.0 mg, 0.10 mmol) in acetic acid (0.6 mL) were added dropwise 48% aqueous HBr (0.9 mL) and DMSO (0.8 mL). The reaction mixture was stirred at room temperature for 44 h. After cooling to 0 °C, the reaction mixture was treated with saturated aqueous solution of NaHCO$_3$ to adjust to pH = 6 and then extracted with EtOAc, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with hexane-CH$_2$Cl$_2$ (9:1) to afford **1d** (10.0 mg, 26%) as a yellow solid. mp = 204−206 °C; IR (neat, cm^{-1}) 2938, 1231, 1056, 1033, 1012, 880, 840, 806, 753; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.36 (t, J = 8.6 Hz, 2H), 8,20, (s, 1H), 7.96−7.87 (m, 4H), 7.77−7.74 (m, 2H), 7.53−7.50 (m, 1H), 7.34−7.30 (m, 1H), 7.18 (dd, J = 8.8, 2.4 Hz, 1H), 3.45 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 157.4, 133.2, 133.8, 131.7, 131.3, 130.7, 130.6, 130.0, 128.9, 128.4, 128.3, 1278.0, 127.0, 126.8, 126.6, 126.4, 124.9, 119.0, 118.6, 110.7, 55.2; HRMS (ESI, Pos) m/z: [M + Na]$^+$ calcd for $C_{23}H_{15}BrNaO$ 409.0198, found 409.0204.

Dibenzo[*c*,*g*]phenanthrene-9,10-diyl Diacetate (2). (a) To a solution of **1b** (30.0 mg, 0.10 mmol) in DMF (0.8 mL) at 0 °C under an argon atmosphere was added 81 mg (0.11 mmol) of stabilized 2-iodoxybenzoic acid (IBX) composition (39% w/w of IBX). The mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was diluted with hexane−EtOAc (4:1), and the organic layers were washed with water and with brine. The organic layers was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude product as a dark red solid. The crude mixture was dried in vacuo for 1 h, and then subjected to the next reaction without further purification. (b) To a crude solution of **9** in DMF (0.5 mL) at 0 °C under an argon atmosphere was added $NaBH_4$ (19 mg, 0.50 mmol). The mixture was allowed to warm to room temperature and stirred for 0.5 h. To the reaction mixture were added acetic anhydride (57 μL, 0.60 mmol) and Na_2CO_3 (64 mg, 0.60 mmol). After 20 h, additional acetic anhydride (57 μL, 0.6 mmol) was added and the mixture was stirred overnight. The reaction was quenched with water at 0 °C. The aqueous layer was extracted and with hexane−EtOAc (4:1). The organic layers were combined, washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with hexane−Et_2O (8:1) to give **2** (27.0 mg, 68%) as an ivory solid. (*P*)-(+)-**2** $[\alpha]_D^{20}$ = +1702 (c 11.3 × 10^{-3}, CHCl$_3$), (*M*)-(−)-**2** $[\alpha]_D^{20}$ = −1665 (c 13.3 × 10^{-3}, CHCl$_3$); mp = 213−215 °C; IR (neat, cm^{-1}); 3276, 2969, 2331, 1764, 1371, 1205, 1159, 1057, 1033, 1012, 841, 746, 675, 659; UV−vis (CHCl$_3$): λ_{max} (log ε) = 309 (4.57), 266 (4.43), 240 (4.49) nm; ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.21 (d, J = 8.5 Hz, 1H), 7.91−7.77 (m, 8H), 7.50 (ddd, J = 8.0, 7.0, 1.0 Hz 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.31 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 2.18 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 168.8, 167.01, 140.8, 139.0, 133.2, 132.6, 132.1, 131.3, 131.0, 128.3, 127.6, 127.4, 127.3, 127.0, 126.9, 126.7, 126.4, 126.1, 126.0, 125.7, 122.3, 121.7, 20.7, 19.3; HRMS (ESI, Pos) m/z: [M + Na]$^+$ calcd for $C_{26}H_{18}O_4Na$ 417.1097, found 417.1135.

Dibenzo[*c*,*g*]phenanthren-10-yl Acetate (3a). To a stirred solution of **3b** (50.0 mg, 0.17 mmol) in CH_2Cl_2 (1.7 mL) at 0 °C under an argon atmosphere were added triethylamine (36.0 μL, 0.25 mmol) and acetic anhydride (24.0 μL, 0.25 mmol). The mixture was allowed to warm to room temperature and stirred for 1.5 h. The reaction was quenched with water at 0 °C. The aqueous layer was extracted and with EtOAc. The organic layers were combined, washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with hexane−Et_2O (5:1) to give **3a** (49.0 mg, 98%) as a white solid. (*P*)-(+)-**3a** $[\alpha]_D^{20}$ = +2046 (c 1.3 × 10^{-2}, CHCl$_3$), (*M*)-(−)-**3a** $[\alpha]_D^{20}$ = −1815 (c 1.3 × 10^{-2}, CHCl$_3$); mp = 155−1157 °C; IR (neat, cm^{-1}) 3462, 2328, 1755, 1203, 838, 751, 671, 659; UV−vis (CHCl$_3$): λ_{max} (log ε) = 309 (4.55), 266 (4.42), 240 (4.41), 270 (4.45) nm; ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.14 (d, J = 8.5 Hz, 1H), 7.94−7.85 (m, 8H), 7.60 (t, J = 7.8 Hz, 1H), 7.52 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 7.26 (ddd, J = 7.8, 6.9, 1.4 Hz, 1H), 7.17 (dd, J = 8.7, 1.1 Hz, 1H), 1.03 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 168.1, 147.9, 134.4, 132.9, 132.8, 131.2, 131.1, 127.9, 127.7, 127.5, 127.1, 127.0, 126.7, 126.3, 125.9, 125.8, 125.7, 125.4, 124.8, 122.3, 119.4, 19.7; HRMS (ESI, Pos) m/z: [M + Na]$^+$ calcd for $C_{24}H_{16}O_2Na$ 359.1043, found 359.1062.

Dibenzo[*c*,*g*]phenanthren-10-ol ((*M*)-(−)-3b and (*P*)-(+)-3b). To a solution of **10** (25.0 mg, 0.05 mmol, dr 20:1) in 2 mL of THF/MeOH (3:1) was added 3 M NaOH (0.5 mL). The reaction mixture was heated at 60 °C for 1 h. After cooling to room temperature, the reaction mixture was neutralized with 10% HCl and extracted with Et_2O. The organic layers were combined; washed with saturated aqueous $NaHCO_3$, water, and brine; dried over $MgSO_4$; filtered; and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with hexane−EtOAc (9:1) to give **3b**. (*M*)-(−)-**3b** (12.9 mg, 88%, 93% *ee*) was obtained from (*M*,*S*)-**10** as a pale yellow foam. (*P*)-(+)-**3b** (13.4 mg, 91%, 91% *ee*) was obtained from (*P*,*S*)-**10** as a pale yellow foam. (*M*)-(−)-**3b**: ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.27 (d, J = 8.6 Hz,1H), 8.00−7.93 (m, 6H), 7.85 (d, J = 8.5 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.59−7.55 (m, 2H), 7.31 (ddd, J = 8.4, 7.1, 1.3 Hz, 1H), 6.95 (dd, J = 7.6, 1.0 Hz, 1H), 5.11 (br s, 1H). (*P*)-(−)-**3b**: ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.27 (d, J = 8.6 Hz,1H), 8.00−7.93 (m, 6H), 7.85 (d, J = 8.5 Hz, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.59−7.55 (m, 2H), 7.31 (t, J = 7.6 Hz, 1H), 6.95 (d, J = 7.6 Hz, 1H), 5.11 (br s, 1H). Spectroscopic data are consistent with our previous report.[1a]

1-Chloro-7-methoxy-3,4-dihydronaphthalene-2-carbaldehyde (5). To a solution of DMF (4.4 mL, 56.70 mmol) at 0 °C was added dropwise $POCl_3$ (4.2 mL, 45.40 mmol). The reaction mixture was warmed to 90 °C and stirred for 1 h to form the Vilsmeier salt. After cooling to 0 °C, 7-methoxy-α-tetralone (**4**) (5.0 g, 28.40 mmol) was added, and the reaction mixture was stirred at 90 °C for 2 h. The reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C. The aqueous layer was extracted and with CH_2Cl_2. The organic layers were combined, washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with hexane−EtOAc (9:1) to afford **5** (5.7 g, 91%) as an orange solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 10.39 (s, 1H), 7.42 (d, J = 2.6 Hz, 1H), 7.14 (d, J = 8.2 Hz, 1H), 6.92 (dd, J = 8.2, 2.6 Hz, 1H), 3.86 (s, 3H), 2.80−2.76 (m, 2H), 2.65−2.60 (m, 2H). Spectroscopic data are consistent with the literature.[15]

7-Methoxy-3,4-dihydro-[1,1′-binaphthalene]-2-carbaldehyde (6). A suspension of **5** (690 mg, 3.1 mmol), 1-naphtylboronic acid (0.58 g, 3.40 mmol), tetrabutylammonium bromide (0.99 g, 3.10 mmol), Pd(OAc)$_2$ (34.0 mg, 5 mol %), and K_2CO_3 (0.85 g, 6.10 mmol) in degassed water (6 mL) was stirred at 45 °C under an argon atmosphere for 1.5 h. After cooling to room temperature, the reaction mixture was diluted with water and extracted with EtOAc. The organic layers were combined, washed with water and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with hexane−EtOAc (9:1) to afford **6** (0.97 g, quant.) as a pale yellow solid. mp = 100−103 °C; IR (neat, cm^{-1}) 2928, 1655, 1566, 1362, 1300, 1232, 1124, 1044, 815, 798, 779, 747, 709; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.38 (s, 1H), 7.92 (dd, J = 12.5, 8.2 Hz, 2H), 7.58−7.46 (m, 3H), 7.42−7.36 (m, 2H), 7.22 (d, J = 8.2 Hz, 1H), 6.81 (dd, J = 8.2, 2.6 Hz, 1H), 6.21 (d, J = 2.6 Hz, 1H), 3.21 (s, 3H), 3.00−2.83 (m, 3H), 2.73−2.64 (m, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 193.0, 158.3, 152.9, 136.3, 136.1, 133.5, 132.7, 132.6, 130.3, 128.9, 128.5, 128.4, 126.8, 126.3, 125.8, 125.0, 114.8, 114.4, 55.1, 26.8, 20.5; HRMS (ESI, Pos) *m*/*z*: [M + Na]$^+$ calcd for $C_{22}H_{18}NaO_2$ 337.1199, found 337.1195.

7-Methoxy-[1,1′-binaphthalene]-2-carbaldehyde (7). To a stirred solution of **6** (1.44 g, 4.60 mmol) in toluene (26 mL) was added DDQ (1.40 g, 5.7 mmol). The resulting solution was heated at 60 °C for 3 h. After cooling to room temperature, the resultant precipitate was removed by suction filtration. The filtrate was washed with 1 N NaOH and extracted with toluene. The organic layers were combined, washed with water and brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with hexane−EtOAc (9:1) to afford **7** (1.43 g, quant.) as a white solid. mp = 75−76 °C; IR (neat, cm^{-1}) 3007, 1688, 1620, 1506, 1454, 1425, 1275, 1178, 1070, 1027, 983, 843, 808, 790, 778, 730; ^{1}H NMR (400 MHz, CDCl$_3$): δ 9.64 (s, 1H), 8.04−7.94 (m, 4H), 7.87 (d, J = 9.0 Hz, 1H), 7.63 (t, J = 7.7 Hz, 1H), 7.53−7.48 (m, 2H), 7.32 (m, 1H), 7.28−7.23 (m,2H), 6.63 (d, J = 7.7 Hz, 1H), 3.49 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 192.5, 158.2, 143.3, 134.3, 133.3, 133.2, 133.1, 132.5, 131.6, 129.6, 129.0, 128.8, 128.3, 126.7, 126.2, 126.0, 125.0, 121.0, 120.0, 106.2, 55.0; HRMS (ESI, Pos) *m*/*z*: [M + Na]$^+$ calcd for $C_{22}H_{16}NaO_2$ 335.1043, found 335.1043.

2-Ethynyl-7-methoxy-1,1′-binaphthalene (8). To a stirred suspension of **7** (3.75 g, 12.0 mmol) and K$_3$PO$_4$ (3.31 g, 15.6 mmol) in MeOH (120 mL) at room temperature under an argon atmosphere was added a solution of Ohira-Bestmann reagent (3.43 g, 15.6 mmol) in MeOH (15.6 mL). The reaction mixture was stirred overnight at the same temperature. After removing the MeOH under reduced pressure, the residue was diluted with EtOAc and washed with H$_2$O. The organic layers were combined, washed with water and brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with hexane−EtOAc (95:5) to afford **8** (3.45 g, 93%) as a pale yellow solid. mp = 87−89 °C; IR (neat, cm^{-1}) 3285, 2970, 1619, 1506, 1458, 1419, 1274, 1258, 1144, 1056, 1033, 844, 781; ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.95 (t, J = 8.8 Hz, 2H), 7.82 (dd, J = 8.7, 6.5 Hz, 2H), 7.70−7.75 (m, 2H), 7.49−7.45 (m, 2H), 7.30−7.29 (m, 2H), 7.15 (dd, J = 9.0, 2.6 Hz, 1H), 6.51 (d, J = 2.4 Hz, 1H), 3.47 (s, 3H), 2.77 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ 158.1, 140.7, 136.6, 134.0, 133.6, 132.4, 129.4, 128.7, 128.1, 128.1, 128.0, 127.5, 126.8, 126.1, 126.0, 126.0, 125.4, 120.6, 119.0, 105.5, 83.3, 80.8, 55.0; HRMS (ESI, Pos) *m*/*z*: [M + Na]$^+$ calcd for $C_{23}H_{16}NaO$ 331.1093, found 331.1105.

Dibenzo[*c*,*g*]phenanthrene-9,10-dione (9). To a solution of **1b** (30 mg, 0.10 mmol) in DMF (mL) at 0 °C under an argon atmosphere was added 81 mg (0.11 mmol) of stabilized 2-iodoxybenzoic acid (IBX) composition (39% w/w of IBX). The reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was extracted with EtOAc, washed with water, dried over anhydrous Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography over silica gel with hexane−Et$_2$O (1:1) to give the compound **9** as a dark red solid (30 mg, 97% yield). mp = 166 °C (decomposition); IR (neat, cm^{-1}) 2923, 2330, 1733, 1389, 1262, 1055, 1033, 1013, 808, 759, 724, 689, 656; UV−vis (CHCl$_3$): λ_{max} (log ε) = 368 (3.42), 351 (3.39), 298 (4.06), 280 (4.07), 243 (4.23) nm; ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.41 (d, J = 8.0 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H) 7.97−7.78 (m, 5H), 7.65 (d, J = 9.6 Hz, 1H), 7.54−7.47 (m, 3H), 6.49 (d, J = 10.0 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 185.0, 184.4, 146.8, 136.3, 135.9, 135.7, 134.8, 133.3, 133.3, 131.8, 130.0, 128.8, 128.7, 128.6, 128.5, 127.8, 127.6, 127.1, 127.0, 126.6, 126.3; HRMS (ESI, Pos) *m*/*z*: [M + Na]$^+$ calcd for $C_{22}H_{12}O_2Na$ 331.0730, found 331.0744.

Dibenzo[*c*,*g*]phenanthren-10-yl ((1*S*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonate ((*M*,*S*)-10 and (*P*,*S*)-10). To a stirred solution of *rac*-3b (48.0 mg, 0.16 mmol) and (1*S*)-camphorsulfonyl chloride (0.10 g, 0.40 mmol) in CH$_2$Cl$_2$ at 0 °C under an argon atmosphere were added triethylamine (81.0 mg, 0.80 mmol) and DMAP (2.4 mg, 0.02 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 15 min. The reaction was quenched with 10% HCl. The resultant solution was neutralized with saturated aqueous NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The organic layers were combined, washed with water and brine, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The diastereomixture was separated by flash column chromatography on silica gel eluting with hexane-Et$_2$O-EtOAc (8:1:1) to afford (*M*,*S*)-**10** (early eluting fraction) as a white foam (35.0 mg, 43%, dr 20:1) and (*P*,*S*)-**10** (late eluting fraction) as white foam (36.0 mg, 44%, dr 20:1). (*M*,*S*)-**10**: $[\alpha]_D^{20}$ = −1350 (c 4.0 × 10^{-3}, CHCl$_3$); mp = 222−225 °C; IR (neat, cm^{-1}) 1747, 1354, 1177, 1160, 1101, 1055, 996, 913, 843, 824, 674, 684; UV−vis (CHCl$_3$): λ_{max} (log ε) = 310 (4.51), 266 (4.40), 240 (4.40) nm; ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.06 (d, J = 8.5 Hz, 1H), 8.00−7.86 (m, 8H), 7.62 (t, J = 7.8 Hz, 1H), 7.54 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 7.46 (dd, J = 7.6, 1.2 Hz, 1H), 7.28 (ddd, J = 8.5, 6.4, 1.4 Hz, 1H), 2.48 (d, J = 14.8 Hz, 1H), 2.24 (ddd, J = 16.9, 3.8, 3.8 Hz, 1H), 1.93−1.88 (m, 2H), 1.81−1.73 (m, 2H), 1.32 (d, J = 14.8 Hz, 1H), 1.29−1.19 (m, 2H), 0.67 (s, 3H), 0.59 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 213.1, 144.8, 134.7, 133.1, 132.6, 131.3, 131.1, 128.2, 128.1, 127.9, 127.8, 127.4, 126.94, 126.90, 126.7, 126.6, 126.3, 125.7, 125.6, 125.5, 125.4, 122.1, 120.9, 57.2, 47.6, 47.1, 42.6, 42.3, 26.7, 24.3, 19.4, 19.3; HRMS (ESI, Pos) *m*/*z*: [M + Na]$^+$ calcd for $C_{32}H_{28}NaO_4S$ 531.1601, found 531.1605. (*P*,*S*)-**10**: $[\alpha]_D^{20}$ = +1100 (c 4.0 × 10^{-3}, CHCl$_3$); mp = 185−188 °C; IR (neat, cm^{-1}) 1747, 1357, 996, 913, 842, 675, 663; UV−vis (CHCl$_3$): λ_{max} (log ε) = 310 (4.55), 266 (4.43), 240 (4.42) nm; ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.07 (d, J = 8.6 Hz, 1H), 8.02−7.87 (m, 8H), 7.62 (t, J = 7.8 Hz, 1H), 7.53 (ddd, J = 8.0, 6.9, 1.1 Hz, 1H), 7.42 (dd, J = 7.7, 1.3 Hz, 1H), 7.29−7.26 (m, 1H), 2.18 (ddd, J = 18.4, 4.7, 2.5 Hz, 1H), 2.00 (d, J = 14.8 Hz, 1H), 1.93−1.79 (m, 3H), 1.73 (s, 1H), 1.69 (d, J = 3.2 Hz, 1H), 1.25−1.22 (m, 2H), 0.78 (s, 3H), 0.58 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$): δ 213.1, 145.5, 134.7, 133.1, 132.6, 131.4, 131.1, 128.3, 128.2, 127.8, 127.7, 127.4, 127.0, 126.9, 126.7, 126.40, 126.35, 125.6, 125.64, 125.58, 124.9, 121.9, 120.5, 57.3, 47.6, 46.9, 42.7, 42.2, 26.7, 24.7, 19.6, 19.4; HRMS (ESI, Pos) *m*/*z*: [M + Na]$^+$ calcd for $C_{32}H_{28}NaO_4S$ 531.1601, found 531.1606.

ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of all new compounds, ORTEP/X-ray and CIF data for single-crystal X-ray analyses of compounds **1d** (CCDC 901873), (*M*, *S*)-**10** (CCDC 1051698), and (*P*, *S*)-**10** (CCDC 1051700), HPLC analysis graphs for enzymatic hydrolysis experiments for compounds **1a** and **2**, kinetic data for racemization for compounds **1a**−**c**, computational details, Cartesian coordinates for all calculated structures, ORTEP drawings of compounds **1d**, (*P*, *S*)-**10**, and (*M*, *S*)-**10**, CD spectra of **1a**, **1b**, **1c**, **2**, **3a**, and **10**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00759.

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Notes

The authors declare no competing financial interest.

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(8) The regioselectivity of oxygen insertion for *rac*-**1b** did not change from that of the 2-naphotol and 3-phenanthrenol building blocks.

(9) The absolute configuration of [5]helicenes was established by the CD exciton chirality method (Figure S1).

(10) Gibbs's free energy barriers to racemization ($\Delta G^{\ddagger}$) of **1a** and **1b** were measured on the basis of the time-dependent conversion rate (% *ee*) estimated from chiral HPLC analysis (Figure S4). The $\Delta G^{\ddagger}$ value at 303 K of **1a** and **1b** were almost the same as that of [5]helicene.

(11) Gibb's free energy barriers to racemization ($\Delta G^{\ddagger}$) of **9** could not be determined because it decomposed. Hence, the racemization barrier of **9** is estimated by DFT (Figure S6).

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